DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 12/03/02

From: Gloria Chang, IDS/Pharmacist, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient: BioVitaflu/BioVitabronch (Vitex negundo, L)

Firm: Kelatron Corp.

Date Received by FDA: 2/11/02

90-Day Date: 5/12/02

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached correspondence for the aforementioned dietary ingredient should be placed on public display in docket number 95S-0316 as soon possible. Thank you for your assistance.

Gloria Chang

Gloria Chang, IDS/Pharmacist

Attachments

95S-0316

RPT117

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD

APR 26 2002

Mary Ann Coral-Amasifuen
Kelatron Corporation World Headquarters
1675 West 2750 South
Ogden, Utah 84401

Dear Ms. Coral-Amasifuen:

This is in response to four separate notifications you submitted pursuant to 21 U.S.C. 350b(a)(2). All four notifications were received by the Food and Drug Administration (FDA) on January 3, 2002, followed by an addendum dated January 10, 2002. In follow up, we contacted you by telephone on January 14, 2002 notifying you that the notifications were incomplete (see background of follow up below). Subsequently, you sent addendums dated January 18, and February 5, 2002. We received your last addendum for your notifications dated February 5, 2002 on February 11, 2002. Therefore, the effective filing date for all four notifications is February 11, 2002.

As noted above, we contacted you by telephone on January 14, 2002 notifying you that the notifications were incomplete in that they did not contain levels of the dietary ingredients, conditions of use, or copies of the full-text journal articles corresponding to the abstracts you sent us. We explained that the requested information would have to be submitted in triplicate (3 copies) if we were to consider these references in our review. On January 24, 2002, we called you again and left a message that the addendums that you sent dated January 18, 2002, did not contain the levels of the new dietary ingredients as requested.

Each notification concerned a different botanical that you assert is a new dietary ingredient. The botanicals are listed below by the Latin binomial name, plant form, and product name as stated in your notifications.

Vitex negundo L. (pure leaf powder) -- BioVitaflu/BioVitabronch
Blumea balsamifera L. (pure leaf power) -- BioRenal
Mormadica charantia L.- Makiling v. (pure leaf powder) -- BioDiamed
Lagerstroemia specious L. (pure leaf powder) -- BioDiamend

The law at 21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor submit certain information to FDA at least 75 days before a new dietary ingredient or a dietary supplement containing it is introduced or delivered for introduction into interstate commerce. This information must include the basis on which the manufacturer or distributor has concluded that the new dietary ingredient or a dietary supplement containing it will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C. 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the product's labeling, will reasonably be expected

to be safe. If this requirement is not met, the new dietary ingredient or dietary supplement containing it is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B), because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has considered the information in your notification and has several significant concerns. Based on the information in your notification for all four botanical ingredients, FDA has determined that the information submitted suggests that the intended uses imply or represent treatment of disease. The following are examples.

- The botanical ingredient *Vitex negundo* L., the product name "BioVitaflu/BioVitabronch" implies a recognizable disease condition, the "flu". FDA considers a brand name that includes a disease name or a clearly recognizable derivation of a disease name to be a disease claim. (See 21 CFR 101.93(g)(2)(iv)(A).)
- Under the conditions of use for the botanical ingredient *Blumea balsamifera* L. (BioRenal) you state that BioRenal might be effective as a diuretic and as an anti-urolithiasis agent (chronic formation of kidney stones).
- Under the conditions of use for the botanical ingredient *Mormadica charantia* L.-Makiling v. (BioDiamed) you state that the recommended use is that it may be helpful for blood sugar regulation and type II diabetes mellitus.
- Under the conditions of use for the botanical ingredient *Lagerstroemia specious* L.-(BioDiamend) you state that clinical trials indicated that BioDiamend may have some blood sugar lowering properties in vivo and therefore the recommended use is that it may be helpful for blood sugar regulation and type II diabetes mellitus.

Please be advised that any representation that a product is intended for the diagnosis, cure, mitigation, treatment or prevention of disease in man or animals suggests that it is a drug, as defined in 21 U.S.C. § 321(g)(1)(B), and would be subject to regulation under the drug provisions of the Federal Food, Drug and Cosmetic Act. All drugs must be approved by FDA before they can be marketed in the United States. If you wish to market your products as drugs, you should contact FDA's Center for Drug Evaluation and Research (CDER), Office of Compliance, HFD-310, 7520 Standish Place, Rockville, Maryland 20855.

FDA also has concerns about the evidence on which you rely to support your conclusion that the four botanical ingredients in your notifications will be reasonably expected to be safe for the suggested or intended uses.

Much of the history of use information you submitted appears to be selected pages printed from commercial magazines or promotional literature. Some of the sources of these articles were not identified nor were the specific ingredients in your notifications mentioned in the articles. These articles primarily focus on anecdotal use for disease conditions and do not address safety. The statements in these articles cannot be validated and are not corroborated

by scientific data. Although requested, you did not provide us with photostatic copies or reprints of all of the abstracts or the complete reference citation for what appears to be an excerpt from a reference book. Consequently, those abstracts and excerpts were not considered in our review.

We are also unsure if the botanical ingredients described in some of the scientific literature were the same as those described in your notifications. Further, we are not sure if the specific genus, species, and author citations are correct for two of the botanical ingredients. Although we searched a number of botanical databases, we could not find the specific Latin binomial names *Mormadica charantia* L. and *Lagerstroemia specious* L as stated in your notifications. We are aware of the Latin binomial names *Momordica charantia* L. or *Momordica charantia* Linn. and *Lagerstroemia speciosa* L. or *Lagerstroemia speciosa* (L.) Pers. However, when referring to your botanical ingredients in this letter, we will be using the Latin binomial names as stated in your notifications.

We also have concerns regarding the scientific information that was submitted. Most of the scientific articles and unpublished reports in your notifications primarily address use of the study ingredients as drugs to treat specific disease conditions and do not provide adequate evidence of the safe use of the specific ingredient. Also, it was not clear if the ingredients used in some of the studies were the same ingredients (genus, species, and author citation), the same part of the plant, or the levels per serving dose, as those stated in your notifications.

In your notification on *Vitex negundo* L (BioFlu/Bio Vitabronch), you submitted a summary of an unpublished, uncontrolled, open label study evaluating the safety and efficacy of *Vitex negundo* L (Lagundi) tablets as an antitussive agent. The trial titled Section 5.2:Phase II Clinical Trial was conducted from January to December 1984. Twenty-five subjects were enrolled, 20 children and 5 adults. Subjects were described as having acute asthma (n=4) or upper-respiratory, non-bacterial infection (n=21). There was a single concluding statement of safety that noted that there were no untoward side effects noted or volunteered. No details or specific data on safety was provided. We also note that the actual dose level in each tablet was not stated. Further, subjects with present or past disease conditions were explicitly not enrolled in the trial as stated in the exclusion criteria of the study. This is of particular concern since under your conditions of use there are no recommendations to restrict its use in persons with pre-existing disease conditions.

In the report of a randomized study comparing lagundi (15 mg/kg taken every 8 hours for 3 days) to theophylline (3 mg/kg taken every 8 hours for 3 days) for the treatment of acute asthmatic exacerbation (a disease condition), forty-three subjects were enrolled, however; 3 subjects dropped out after 24 hours. Twenty of the subjects were exposed to lagundi. The analysis was done on forty subjects, 6 males and 34 females. For almost all outcome measures the theophylline group was superior to the lagundi group. Adverse events were noted for 8 theophylline subjects and 5 in the lagundi group. In the lagundi group, the side effects noted were emesis (2 cases), palmar desquamation (2 cases) and increased urinary frequency (1 case). The author did not comment on the subjects that developed palmar

desquamation. The author also expressed concerns about the inadequacy of this study and recommended further evaluation and investigation of lagundi.

We also have concerns regarding the short exposure time to lagundi. The total clinical exposure cited as a safety database consists of only approximately 45 individuals with only a maximum exposure to lagundi of 72 hours. Considering that you did not indicate any limitation or duration of use, these studies do not address chronic use or long term use. Further, we have concerns that subpopulations with present or past medical conditions that were excluded in the study, were not recommended for exclusion under your conditions of use. Accordingly, the study cannot support the conclusion that lagundi is reasonably expected to be safe if marketed as a new dietary ingredient for the intended or suggested use.

In the notification for *Blumea balsamifer* L. (BioRenal), you submitted sections of a larger unpublished study labeled as "7.0 CLINICAL TRIALS." The subsections are; 7.1 "Phase I: Sambong Tablet as Diuretic", 7.2 "Phase II:Clinical Trial of Sambong Tablet as Diuretic," 7.3 "Phase II:Sambong Tablet as anti-urolithiasis," 7.4, "Phase III clinical Trial of *Blumea balsamifer* L (Sambong) tablet in the treatment of urinary tract stone: a randomized double-blind placebo-controlled study", and 7.5 "Extended Phase III Open Trial of *Blumea balsamifer* L (Sambong) for the treatment of urinary tract stones."

All of the studies were small. Overall, 59 subjects were exposed to Sambong across all 5 studies. Exposure time ranged from 2 days to a maximum of approximately 6 weeks. Most of the exposures were less than 6 weeks.

In the studies for diuretic use, we have the following specific comments. No mechanism for the diuretic activity was ascertained, yet based on the conclusions reached that the diuretic effect of Sambong was comparable to thiazide diuretics, Sambong use may pose a safety risk in a normal population or in a subpopulation who may be also using other diuretics. The studies did not sufficiently address safety. Based on the conclusions in the study that Sambong tablets produced statistically significant diuresis and chloriuresis comparable to hydrochlorthiazide given at 50 mg in 2 divided doses, we have concerns that this may pose an electrolyte imbalance risk in normal populations or in a subpopulation with certain present or past medical conditions. Your recommended conditions of use only excluded use in lactating or pregnant women. Your recommended use in adults 18 years old and over neither included instructions on limitations or duration of use nor excluded use for any other populations that may be at risk either for using diuretics or due to concurrent use of other diuretic agents.

In addition, we have concerns regarding the implied use of BioRenal to treat or prevent kidney stones, a disease condition. We have significant safety concerns that consumers will not be able to self diagnose this specific disease condition and that prolonging medical treatment may lead to more serious health consequences.

In your notification for *Mormadica charantia* L.- Makiling v. (BioDiamed), the only full text journal article, was a general summary on the anti-diabetic properties and phytochemistry of a

botanical *Momordica charantia* L. Please note the difference in the Latin binomial names for your botanical ingredient and the botanical cited in the article. The article primarily focuses on general efficacy, and not the safety of the seeds or juice of the plant. It does not address the specific plant part or form (the pure leaf powder) or the serving levels as that of your ingredient. Further, the *in vivo* animal studies information presented a general overview of referenced toxicity studies and focused primarily on the juice or extracts of Karela. You did not provide the referenced full text journal articles in your notification. We are unsure if Karela is the same plant source or plant form as your ingredient. Nonetheless, the animal toxicity information did not provide any dosing levels used nor did it address the specific plant form described in your notification.

Thus, we conclude that the evidence of safety from the article was minimal or lacking and no conclusions of safety can be drawn from the report. We also cannot draw any safety conclusions from the other published report on the hyperglycemic activity of polypeptides of a plant source (fruit, seeds, and tissue). That report focuses on a peptide isolated from the seeds and tissue of a botanical variety, *Momordica charantia* Linn. and does not describe the specific plant part (pure dried leaf powder) described in your notification. Further, the report primarily addresses hypoglycemic activity of the peptide and the only safety information is a statement that referenced a study using a polypeptide-p-ZnCl in three juvenile patients. A photostatic copy or reprint of the full published text of that citation reference was not included in your submission. Thus, no conclusions regarding safety can be drawn from the report.

In your notification for *Lagerstroemia specious* L., the study submitted appears to be an unpublished trial titled "The Clinical Study on the Water Extract of Leaves of *Lagerstroemia specious* L for Mild Cases of Diabetes Mellitus." Twenty-four subjects over the age of 20 years were studied. There is very little information on safety in this report and it is unclear if the study was a single or double-blinded study, a critical concern in safety analysis. The only statement regarding safety was a statement that all 24 subjects did not have any adverse effects. In the absence of detailed safety data and the small size of the study, there is very little evidence to conclude that the ingredient can be reasonably expected to be safe for its intended or suggested use.

Overall, the evidence of safety provided for all four of the dietary ingredients submitted is either minimal or lacking. All of the supporting studies were of a short duration, without any evidence demonstrating safety with chronic exposure. You indicated that under conditions of use these ingredients in general, were to be recommended for use in adults (18 and over) and were not to be used by lactating or pregnant women. However, the study exclusion criteria specifically excluded subpopulations with certain medical conditions from the studies. This may be of particular concern, because under your conditions of use you did not indicate any limit or duration of use for the four botanicals and persons excluded from clinical trials are not excluded under your recommended conditions of use.

We have determined that the history of use information you submitted in all four of your notifications has limited utility in evaluating the safety of these ingredients if marketed as

dietary supplements. In conclusion, the information in your notifications does not provide an adequate basis to conclude that *Vitex negundo* L., *Blumea balsamifera* L., *Mormadica charantia* L.- Makiling v., and *Lagerstroemia specious* L. are reasonably expected to be safe when used under the recommended or suggested conditions of use. Therefore, any product containing any of the botanicals listed in your notifications as *Vitex negundo* L., *Blumea balsamifera* L., *Mormadica charantia* L.- Makiling v., and *Lagerstroemia specious* L. may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains one or more new dietary ingredients at levels for which there is inadequate information to provide reasonable assurance that they will not present a significant or unreasonable risk of illness or injury. Adulterated or unsafe dietary supplements are prohibited under 21 U.S.C. 331(a) and (v) from being introduced or delivered for introduction into interstate commerce.

Your notifications will be kept confidential for 90 days after the filing date of February 11, 2002. After May 11, 2002, the four notifications will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information in the notifications will not be disclosed to the public.

Prior to May 11, 2002, you may wish to identify in writing specifically what information in your notifications you believe is proprietary for FDA's consideration. Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notifications should be redacted before they are posted at Dockets.

If you have any questions concerning this matter, please contact us at (301) 436-2371.

Sincerely yours,

Felicia B. Satchell

Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

KELATRON CORPORATION
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Phone. 801-394-4558 • Fax: 801-394-4559
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email biomm@kelatroncorp.com

Mr. Gary Coody
Office of Nutritional Products
Labeling and Dietary Supplements (HFS-805)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Md. 20740

Dear Mr. Coody,

In reference to the submission of information on the botanicals trademarked **Biodiamed, Biodiamend Biorenal and Biovitabronch/Biovitaflu** in accordance with the regulation:
TITLE: 21 Food And Drugs
Chapter I – Food and Drug Administration
Dept of Health and Human Services
Part 190 – Dietary Supplements
Subpart B—New Dietary ingredient Notification
Sec. 190.6 Requirement for premarket notification

Please accept the enclosed modified pages which include *Directions* (for use) under the *Condition of use* clause.
Also enclosed are additional materials (clinical trial data)on Biorenal for your review.
I believe this was the missing information.

Please call me directly at my office in North Carolina, 252-234-7160 if further information is needed.

Thank you,

Mary Ann Coral-Amasifuen

From:
Mary Ann Coral-Amasifuen
Kelatron Corporation World Headquarters
1675 West 2750 South
Ogden, Utah 8440
Phone (801) 394-4558

Kelatron Corporation Botanical Division
2145 Barefoot Park, SW
Wilson, North Carolina 27893
Phone: (252) 234-7160

To:
Office of Nutritional Products
Labeling and Dietary Supplements (HFS-805)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Md. 20740
Atten: Gary Coody

In accordance with:
TITLE: 21 Food And Drugs
Chapter I – Food and Drug Administration
Dept of Health and Human Services
Part 190 – Dietary Supplements
Subpart B—New Dietary ingredient Notification
Sec. 190.6 Requirement for premarket notification

(1) **Name and address of distributor**: Kelatron Corporation
1675 West 2750 South
Ogden, Utah 84401

(2) **Name of new dietary ingredient:** BioVitaflu / BioVitabronch (*Vitex negundo*, L)

(3) **Description of new ingredient:** BioVitaflu / BioVitabronch is the bulk pure leaf powder of the plant variety *Vitex negundo*, L. harvested for medicinal purposes in the Philippines. There has been clinical research done on the effectiveness of this plant for enhancing air flow in and out of lungs and reducing phlegm caused by congestion in the lungs. It is currently in use in the Asian market under the name Lagundi, which is the local name for the plant in southeast Asia.

(3) (i) **Level of new ingredient**: The product contains only the pure plant leaf powder of *Vitex negundo*, L and no other substance, to be sold in bulk powder form to retail manufacturers.

(3) (ii) **Condition of use**: : In general, to be used by adults (18 and over). Not to be used by lactating or pregnant women. Directions: One 600 mg capsule three times per day

(4) **History of use** *see attachment 4A*

(5) **Signature** _____ **Date** 2-5-02

January 18, 2002

MR. Coody,

I have made corrections to the Conditions of use portion in three of the applications.

We will send the full text article and remaining Condition of use modification when I arrive back to my office in North Carolina.

It would be helpful if you would log in the botanical products that are in Compliance with the information requested.

Thank you,

Mary Ann Cook-Gonsalves

From:
Mary Ann Coral-Amasifuen
Kelatron Corporation World Headquarters
1675 West 2750 South
Ogden, Utah 8440
Phone (801) 394-4558

Kelatron Corporation Botanical Division
2145 Barefoot Park, SW
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Phone: (252) 234-7160

To:
Office of Nutritional Products
Labeling and Dietary Supplements (HFS-805)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Md. 20740
Atten: Gary Coody

In accordance with:
TITLE: 21 Food And Drugs
Chapter I – Food and Drug Administration
Dept of Health and Human Services
Part 190 – Dietary Supplements
Subpart B—New Dietary ingredient Notification
Sec. 190.6 Requirement for premarket notification

(1) **Name and address of distributor**: Kelatron Corporation
1675 West 2750 South
Ogden, Utah 84401

(2) **Name of new dietary ingredient:** BioVitaflu / BioVitabronch (*Vitex negundo*, L)

(3) **Description of new ingredient:** BioVitaflu / BioVitabronch is the bulk pure leaf powder of the plant variety *Vitex negundo,* L. harvested for medicinal purposes in the Philippines. There has been clinical research done on the effectiveness of this plant for enhancing air flow in and out of lungs and reducing phlegm caused by congestion in the lungs. It is currently in use in the Asian market under the name Lagundi, which is the local name for the plant in southeast Asia.

(3) (i) **Level of new ingredient**: The product contains only the pure plant leaf powder of *Vitex negundo*, L and no other substance, to be sold in bulk powder form to retail manufacturers.

(3) (ii) **Condition of use**: : In general, to be used by adults (18 and over). Not to be used by lactating or pregnant women.

(4) **History of use**: *see attachment 4A*

(5) **Signature** _____ **Date** 1-18-02

addendum
(note: some duplicated

From:
Mary Ann Coral-Amasifuen
Kelatron Corporation World Headquarters
1675 West 2750 South
Ogden, Utah 84401
Phone (801) 394-4558

Kelatron Corporation Botanical Division
2145 Barefoot Park, SW
Wilson, North Carolina 27893
Phone: (252) 234-7160

To:
Office of Nutritional Products
Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

In accordance with:
TITLE: 21 Food And Drugs
Chapter I – Food and Drug Administration
Dept of Health and Human Services
Part 190 – Dietary Supplements
Subpart B—New Dietary ingredient Notification
Sec. 190.6 Requirement for premarket notification

(1) **Name and address of distributor**: Kelatron Corporation
1675 West 2750 South
Ogden, Utah 84401

(2) **Name of new dietary ingredient:** BioVitaflu / BioVitabronch (*Vitex negundo*, L)

(3) **Description of new ingredient:** BioVitaflu / BioVitabronch is the bulk pure leaf powder of the plant variety *Vitex negundo,* L. harvested for medicinal purposes in the Philippines. There has been clinical research done on the effectiveness of this plant for enhancing air flow in and out of lungs and reducing phlegm caused by congestion in the lungs. It is currently in use in the Asian market under the name Lagundi, which is the local name for the plant in southeast Asia.

(3) (i) **Level of new ingredient**: The product contains only the pure plant leaf powder of *Vitex negundo*, L and no other substance, to be sold in bulk powder form to retail manufacturers.

(3) (ii) **Condition of use**: Clinical trials indicated that BioVitaflu/BioVitabronch may be effective in relaxing smooth muscle tissue and ease night time coughing.

(4) **History of use**: *see attachment 4A*

(5) **Signature** Mary Ann Coral **Date** 1·10·02

LAGUNDI

(*Vitex negundo* L.)

ORIGINAL ARTICLE:

THE EFFECT OF "LAGUNDI" (a local herb) TABLETS ON BRONCHIAL ASTHMA IN ADULTS: RANDOMIZED DOUBLE BLIND STUDY WITH THEOPHYLLINE*

By: Romeo P. Chu, M.D.**

ABSTRACT

Forty otherwise healthy asthmatics were included in a randomized double blind comparative study between lagundi tablets and the standard drug theophylline. There were 20 subjects per treatment group; 7 of the subjects were males and 33 females. The patient profile of both treatment groups were comparable. Likewise, the baseline parameters of both groups were also comparable. Results showed that both lagundi and theophylline caused significant bronchodilation over time. Statistical analysis showed significant increase in the mean peak expiratory flow rate (PEFR) of the lagundi group beginning at the 3rd hour. This shows the onset of action of lagundi to be at 3 hours postdosing. For the theophylline group, significant increase in the PEFR values was noted at 1 hour which corresponds to its onset of action. ANOVA with repeated measures showed no significant difference between lagundi and theophylline with respect to their effects on PEFR. However, since the sample size is inadequate, it cannot yet be concluded that lagundi is as effective as theophylline. Patients treated with lagundi failed to show a significant improvement of their wheezing over time but might have prevented the wheezing from getting worse. Patients treated with theophylline however showed significant improvement of their wheezing as early as the second hour. The theophylline treated patients had significantly better wheezing scores than the lagundi group at the 6th, 8th, 24th and 48th hour. There were no significant difference in the severity of cough, dyspnea and chest pain in both treatment groups over time. However, the theophylline treated group had better "cough" than the "lagundi" group at the 24th and the 48th hour. The theophylline group had also better "dyspnea" scores than the lagundi group at the 48th hour. There was no significant difference between lagundi and theophylline in terms of the effects on pulse rate, respiratory rate and blood pressure (BP) readings. However, there was significant decrease in the mean sitting systolic BP and standing diastolic BP over time. This needs further investigation. Side effects reported in the lagundi group were vomiting, desquamation of the skin over the palms and increased frequency of urination. In the theophylline group, the side effects reported were nausea, vomiting, cold sweats, palpitations, tremors, headache and epigastric pain. Overall, lagundi displayed significant bronchodilating effects. Although theophylline has a slight edge in terms of therapeutic efficacy, lagundi still holds to be a promising drug in the future.

INTRODUCTION

The use of plants for medicinal purposes is as old as man himself. Primitive man probably learned their medicinal value from intuition and observation of the animals around him. Through trial and error, he discovered the efficacy of certain plants for certain ailments and he passed this knowledge on to his neighbors. From such beginnings sprung our present knowledge of the use of plant constituents in the treatment of disease.

Philippine flora abounds with plants of medicinal value. Scientific proof of efficacy, established through the isolation of their active

* *FIRST PRIZE winner, 6th PAFP-SANDOZ RESEARCH CONTEST, Feb. 19, 1988, Manue Midtown hotel*

** *Resident Physician, Dept. of Family Medicine (1985-87), Philippine General Hospital, Manila, Philippines*

constituents and studies on their pharmacologic actions, has been accomplished on some of these plants. This work was done principally by the University of the Philippines, the National Institute of Science and Technology (NIST) and the Philippine Council for Health Research and Development (PCHRD). However, there remains a large number of plants, widely used in folk medicine, still to be investigated. One of these plants is Lagundi.

Vitex negundo (Lagundi, Tag.) is an erect, branched shrub which grows throughout the Philippines. It is found more commonly in low and medium altitudes and in waste places, thickets, and similar locations. The leaves usually have 5 leaflets (rarely 3) which are palmately arranged. These leaves are found to have an essential oil and resin, while the fruit contains an acid resin and an astringent organic acid. The leaves and seed of the plant were first reported as a medicine by Fr. Clain. Thereafter, more medicinal uses for the plant have been reported, among which are: as cleanser for ulcers, as lactagogue, febrifuge, expectorant, wound disinfectant and for flatulence. The leaves in particular have been used as insecticide, anti-inflammatory, expectorant, and for catarrh and headache.

Open clinical trials have shown that the decoction of leaves of lagundi decreased the frequency of cough and increased the volume of expectoration. In a study in guinea pigs, using citric acid as cough inducer, the antitussive effect of the decoction was comparable to that of dextrometorphan.

Anecdotal reports seem to show a favorable response of asthmatic patients to lagundi leaves decoction. The bronchodilating activity of lagundi leaves has repeatedly been shown using the cat tracheal chain model. One child in acute asthma showed improvement of FEVI, FVC and PEFR after a single dose of lagundi leaves decoction.

OBJECTIVES:

1. To determine the therapeutic efficacy of lagundi tablets on bronchial asthma in adults.
2. To compare the effect of lagundi tablet to that of theophylline tablet on bronchial asthma.
3. To determine the onset of action of the bronchodilating activity of lagundi tablet on bronchial asthma.
4. To compare the adverse effect/s of lagundi tablets (if any) to that of theophylline tablets on bronchial asthma.

METHODOLOGY:

A. Preparation of Test Drugs

1. Lagundi tablets made from pulverized dried lagundi leaves were manufactured by PCHRD. The tablets utilized were from lot no. 28108601.
2. Theophylline tablets (125 mg/tab) were street purchased.

B. Selection of Patients

1. Inclusion criteria:

a. Males and females 14 years and above with definite history of asthma.

b. Patients whose PEFR is less than 85% of predicted value and who are able to demonstrate that their bronchospasms is reversible in the following manner:

The patient's peak expiratory flow rate is recorded before and 15 minutes after 2 inhalations of a metered dose (100 mcg) of salbutamol aerosol. Only patients whose PEFR is increased by 20% will be admitted to the study.

c. Except for asthma, patients must be in good general health.

d. Patients who have been fully informed of the possible risks and benefits of participation and have voluntarily agreed to participate in this study. For minors, parents or guardians who are fully informed shall also sign the consent.

2. Exclusion criteria:

a. Patients with severe asthma as defined:
1. grade 2A or worse (see Appendix A)
2. presence of resting tachycardia
3. pulsus paradoxus k 20 mmHg
4. PEFR 120 or less
5. impending ventilatory failure

b. Patients who require maintenance doses of any medications other than the test drug. Patients on beta – 2 agonist agents and short or long acting theophylline preparations are required to stop medications at least 24 hours prior to the study.

c. Patients who have used systemic steroids chronically within six months before entry into the study; or have used a single dose of dexamethasone or betamethasone within six weeks before entry into the study; or have used systemic short acting steroids within 14 days before entry into the study.

d. Patients who have used disodium cromoglycate or ketotifen within seven days before entry into the study.

e. Patients with any of the following:

1. cardiac arrhythmia
2. moderate to severe hypertension
3. patients on beta blocker therapy
4. insulin dependent diabetes mellitus
5. significant hepatic or renal disease

f. Patients who are pregnant or lactating.

C. Study Design

This is a double blind standard drug controlled study utilizing 40 patients who are randomly assigned to 2 groups: Group 1 (20 patients) to receive theophylline (3 mg./kg./dose) repeated every 8 hours for 9 doses. Group 2 (20 patients) to receive lagundi (15 mg./kg./dose) repeated every 8 hours for 9 doses.

After a patient has been selected as a candidate for the study and has given informed consent, the following procedures were performed.

1. complete medical history and physical examination with emphasis on PEFR, sitting and standing blood pressure, respiratory rate, pulse rate and auscultation of the chest.

2. routine laboratory tests:

a. hematology: hemoglobin, hematocrit, total white cell count, differential count, erythrocyte sedimentation rate, reticulocyte count and platelet count.

b. blood chemistries: BUN, creatinine, SGPT, RES

c. urinalysis

3 chest x-ray (optional)

In all patients enrolled into the study, sufficient time was allowed for recovery from the salbutamol test (at least 8 hours). Once the PEFR is again less than 85%, then the study is resumed.

During the course of the study, all food substances must be caffeine-free. No coffee, tea, chocolate or softdrinks were allowed.

Prior to giving of medications (baseline) and at 15 minutes, 30 minutes 1, 2, 3, 4, 6, 8, 24, 48 and 72 hours post-dosing, the following were examined (or asked) and properly recorded:

1. sitting and standing blood pressure
2. pulse rate
3. respiratory rate
4. PEFR at standing position (the highest of at least 3 acceptable efforts was recorded)

5. chest auscultation noting the degree of wheezing scored as follows: none – 0; mild -1; moderate – 2; severe – 3.
6. severity of cough scored as above
7. degree of dyspnea scored as above
8. degree of chest pain scored as above

Side effects or adverse reactions were described and properly recorded.

D. Intercurrent Events

Patients were not allowed to take concomitant medications during the study. If the patient does not respond to either lagundi or theophylline, then salbutamol tablets at a maximum dose of 2 mg. every 8 hours will be added to the regimen and recorded.

DATA ANALYSIS

Analysis of variance (ANOVA) with repeated observations with respect to time was used for data on theophylline and lagundi doses for the four variables: blood pressure, pulse rate, respiratory rate and PEFR. If a statistically significant result is obtained, Duncan Multiple Range Test was employed to determine the specific periods of observation which are significantly different from baseline.

Friedman two way analysis of variance was employed to determine if there was significant difference in the severity of cough, wheezing, dyspnea and chest pain over time.

Mann-Whitney U Test was used to determine if there was significant difference between the two treatment groups with respect to their effect on the severity of wheezing, cough, dyspnea and chest pain.

RESULTS AND DISCUSSION

From Sept. 22 to Dec. 31, 1987, 43 subjects participated in the clinical trial. 3 dropped out of the study after 24 hours. All of them were in the theophylline group. The first one dropped out to take care of her sick child; the second due to inclement weather (typhoon) and the third for unknown reason. Only 40 subjects were included in the following discussion.

Patient Profile

The 40 subjects were equally distributed for each treatment group – 20 in the lagundi group and 20 in the theophylline group. There were 7 males and 33 females with a ratio of 1:4.7. In the lagundi group, there were 19 females and only 1 male while in the theophylline group, there were 14 females and 6 males.

The mean age for the lagundi group (31.2 years) was slightly lower than the theophylline group (34.7 years). The mean age for all subjects was 32.95 years. The age range for the lagundi group was from 20 to 48 years while that of the theophylline group was from 16 to 72 years. Mean duration of illness for the lagundi group was 13.3 years while that of the theophylline group was 18.1 years. The mean duration of illness for all subjects was 15.7 years. The frequency of attacks was similar for both groups which ranged from weekly to yearly. All the subjects included in the study had previously been taking either a theophylline preparation, beta-2 agonist agents, or both. There were 3 subjects with concomittant illness. 2 patients in the lagundi group had mild hypertension and 1 patient in the theophylline group had nodular non-toxic goiter.

Laboratory Tests Results

All blood chemistries were within normal limits except for 2 patients. One of these is in the lagundi group and has a WBC count of 13,000/mm3. The other patient is in the theophylline group and has a WBC count of 10,000/mm3. Both have normal differential counts and had no clinical evidence of infection.

2 patients in the lagundi group has slightly elevated eosinophil count at 0.04 x 109/L. 2 patients in the theophylline group also showed elevations at 0.03 and 0.07 x 109/1 respectively.

25 out of the 40 subjects had their chest x-ray done within the year. All showed normal findings except for 4 patients. 2 patients showed minimal infiltrates in the upper lung fields interpreted as minimal pulmonary tuberculosis activity undetermined, one of these belong to the lagundi group while the other was in the theophylline group. One of the patients in the lagundi group had a chest x-ray which showed emphysematous changes while the other patient in the theophylline group showed streaky densities on both lower lung fields interpreted as chronic non-specific inflammatory disease.

Figure 1 illustrates graphically the mean PEFR values of both the lagundi and theophylline treated groups over time.

The analysis of variance (ANOVA) with repeated measures showed a significant difference in the mean PEFR values of both treatment groups over time. This means that both drugs, lagundi and theophylline, caused significant bronchodilation over time. Duncan multiple range test showed significant increase in the mean PEFR values (from baseline fo 238.75 L/min.) of the lagundi group beginning at the

third hour reaching 257.5 L/min. (This was sustained up to 8 hours). This means that the onset of action of lagundi is at 3 hours post-dosing. For the theophylline group, significant increase in the PEFR value was noted at 1 hour (from a baseline of 257.75 L/min. to 288.75 L/min.) which corresponds to its onset of action. This effect was sustained throughout the study period.

Comparing the 2 drugs in terms of their effect on the PEFR values using the ANOVA with repeated measures, the results showed no significant difference between the two treatment groups at $P > 0.05$. However, since the sample size is still inadequate, it cannot yet be concluded that lagundi is as effective as theophylline.

Figure 2 illustrates graphically the mean pulse rate of both treatment groups over time. ANOVA with repeated measures showed no significant difference in the pulse rate of both treatment groups over time. This means that both drugs are safe in that they do not significantly affect the pulse rate. They are neither myocardial stimulants nor depressants.

There was also no significant difference between the two drugs in terms of their effect on the pulse rate.

Figure 3 illustrates graphically the mean respiratory rate (RR) of both treatment groups over time. The ANOVA showed no significant difference in the mean RR of both treatment groups over time. This could be so because most patients included in this study had only mild asthma and are thus not tachypneic. In fact, the mean RR for all subjects was only 20.5/min. Even if the patients responded to the medications and had relief of their bronchospasm, no significant drop in the RR is expected because of the above stated reason. What is important to note is that the mean RR did not increase which means that the patients did not get worse.

Figure 4 illustrates graphically the mean sitting blood pressure (BP) of both treatment groups over time. There was significant difference in the mean sitting systolic BP over time for both treatment groups. In the lagundi group, the mean baseline systolic BP at sitting position was 109.75 mmHg. At 30 mins. and at the 6th hour, this was significantly lower at 30 mins. with a mean reading of 106.9 mmHg. This was also noted at the following observation periods: 2 hours (hrs.), 4 hrs., 5 hrs., 6 hrs., 8 hrs. and 72 hrs. These changes could be due to the relief of bronchospasms or due to the fact that the patients were rested for a longer period of time. It is also important to note that although there was a significant decrease in the sitting systolic BP, this effect was not consistent throughout the study periods. No patient reached hypotensive levels nor were there complaints of dizziness attributable to the decline in BP. All these plus the fact that all patients (except for the 2 previously mentioned hypertensives) were normotensive seem to point out that these differences were not really that important. These findings were also not consistent in the 2 patients (both in the lagundi group) with mild hypertension. One patient had a slight increase in systolic BP while the other had a slight decrease.

Comparing the two, there was no significant difference between lagundi and theophylline in terms of their effect on sitting systolic BP.

For the sitting diastolic BP, there was no significant difference in both treatment groups over time. There was also no significant difference between the two groups in terms of their effect on sitting diastolic BP.

Figure 5 illustrates graphically the mean standing BP readings of both treatment groups over time.

ANOVA with repeated measures showed no significant difference in standing systolic BP readings of both treatment groups over time. There was also no significant difference between the two drugs in terms of their effect on standing systolic BP.

There was a significant decrease in the mean standing diastolic BP for both treatment groups over time. For the lagundi group, the baseline mean diastolic BP in standing position was 84 mmHg and there was a significant decrease to 77 mmHg noted at the 4th hour up to the 8th hour and at the 24th hour. For the theophylline group, the baseline mean standing diastolic BP was 79.8mmHg which significantly decreased to 75 mmHg at 30 mins., the 1st hour and the 4th hour. Again, the reasons previously cited could be used to explain the significant decrease in BP readings, i.e. – relief of bronchospasm and longer period of rest. Similarly,

the significant decrease was not persistent throughout the study period and that the patients did not reach hypotensive levels.

Chest Findings

The study shows that in the severity score for wheezing in the lagundi group over time, the higher the rank sum, the more severe is the wheezing. Note that the changes in the scores are minimal. Using the Friedman 2 way ANOVA, there is no significant difference in the severity of wheezing at $P > 0.05$. This means that patients treated with lagundi failed to show a significant improvement of their wheezing over time but might also mean that lagundi prevented their wheezing from getting worse.

The severity scores for wheezing in the theophylline group over time showed results of statistical analysis indicating significant improvement in the severity of wheezing at $P > 0.05$. This was noted as early as the second hour and was sustained throughout the study period.

Mann Whitney U test was utilized to compare the two treatment group with respect to their effects on wheezing. There was a significant difference between the lagundi and theophylline treated group at the 6th hour, 8th hour, 24th hour and 48th hour. This means that the improvement in the severity of wheezing in the theophylline treated group was significantly better than the lagundi group at the observation period stated above.

Cough

Statistical Analysis of the severity scores for cough in the lagundi group over time showed no significant difference in the severity of cough in this treatment group at $P > 0.05$. This means that patients treated with lagundi failed to show significant improvement or deterioration of their cough over time. A larger sample size might be able to detect a significant difference. Although previous studies showed lagundi to be effective against cough of viral origin, the parameters used was more of frequency rather than severity, so the results are not quite comparable.

Statistical analysis of the severity scores for cough in the theophylline treated group over time also showed no significant difference in the severity of cough in this treatment group over time at $p > 0.05$. Although theophylline afforded significant relief of bronchospasm and improvement of wheezing, there is still no significant improvement of its associated cough. A larger sample size might be able to detect a significant difference.

Comparing the two treatment group with respect to their effect on cough, there is a statistically significant difference between the lagundi group and the theophylline group at the 24th and 48th hour. This means that the improvement in the severity of cough in the theophylline treated group was significantly better than the lagundi treated group at the above stated observation periods.

Dyspnea

Statistical analysis of the severity scores for dyspnea in the lagundi treated group over time showed no significant difference in the severity of dyspnea in this treatment group over time at $p > 0.05$. This means that although patients treated with lagundi had significant relief of their bronchospasm, yet there was no significant improvement in the severity of their dyspnea. However, lagundi might have protected them from getting worse.

With regards the severity scores of dyspnea in the theophylline treated group over time, statistical analysis showed no significant difference in the severity of dyspnea in this treatment group over time at $p > 0.05$. This means that the degree of dyspnea in patients treated with theophylline neither improved nor worsened.

Comparing the two treatment groups with respect to their effect on dyspnea, there was a statistically significant difference between the lagundi group and the theophylline group at the 48th hour. This means that the improvement in the severity of cough in the theophylline treated group was significantly better than the lagundi treated group at the observation period stated above.

Chest Pains

Friedman 2 way ANOVA showed no significant difference in the severity of chest pains over time for the lagundi group at $p > 0.05$. This means that patietns treated with lagundi failed to show a significant improvement or worsening of their chest pain over time.

For the severity scores for chest pain in the theophylline group over time, statistical analysis showed no significant difference in the severity of chest pains over time for this treatment group at $p > 0.05$. This means that patients treated with theophylline failed to show a significant improvement or worsening of their chest pain over time.

Comparing the two treatment groups with respect to their effect on chest pains, there is no significant difference between the lagundi group and that of the theophylline group at any observation period. No t one drug is superior to the other with respect to their effect on chest pain.

Number of Salbutamol Tablets

Twelve patiens (30% of the sample size) took salbutamol tablets after 24 hours because they developed asthmatic attacks. Eight (8) were in the lagundi group and four (4) in the theophylline group. Of the 8 subjects in the lagundi group, 1 patient took 8 Salbutamol tablets (This patient had been on prednisone for 10 days but has stopped since 3 weeks prior to the study and had fair control of her asthma. He bronchial airway hyper-reactivity might have flared up again); 1 patient took 4 tablets; another patient took 2 tablets and 3 patients took 1 tablet each. The total number of salbutamol tablets taken in the lagundi group was 27. Of the 4 patients in the thophyllinine group, 1 patient took 3 tablets and 3 patients took 1 tablet teach. Total number of salbutamol tablets taken in the theophylline group was only 6. No statistical analysis was employed to analyze the difference between the two treatment groups in terms of the number of additional medications taken but it seems apparent that theophylline patients fared better than the lagundi patients in that they took less salbutamol tablets.

The fact that these patients took salbutamol tablets did not invalidate the previous conclusions drawn for the above parameters, regardless of the treatment groups. All patients took these additional medications after the first 8 hour observation period which leaves us to account only for the 24th, 48th and 72nd hour. Reviewing the individaul charts however showed that all parameters went down (reflecting worsening condition) during these three observation periods even if the patients took salbutamol tablets in contrast to the general trend which shows that the parameters were going up (reflecting improving condition). This means that the intake of salbutamol tablets did not contribute significantly enough to alter the results of the different parameters under study.

Adverse Effects

Two (2) patients in the lagundi group complained of vomiting; another 2 noted desquamation of the skin over their palms and another one complained of increase frequency (but not amount) in urination.

Three (3) patients in the theophylline group complained of nausea and one of them vomitted; 2 complained of cold sweats and palpitations; another 2 complained of headaches; 1 complained of epigastric pain and another one complained of dizziness.

CONCLUSION AND RECOMMENDATIONS

Results of this study showed that lagundi caused significant bronchodilating activity and had fewer side effects. Although theophylline has a slight edge in terms of therapeutic efficacy, yet lagundi still holds to be a promising drug in the future. The lagundi tablets used were but made from crude dried leaves and might contain only minimal active compounds. Thus, the dosage used although at 15 mg/kg./dose might actually be inadequate. Further investigations must be undertaken and the following steps are recommended.

1. Active principle should be isolated.
2. Studies should be done correlating bronchodilation with serum levels.
3. Pharmacokinetics and pharmacodynamics of lagundi should be studied.

The increasing uses of medicinal plants, the present return to Mother Earth and nature's product, the number of people from all over the world who rely partly or completely on herbal cures and the success they achieve, are clear indications of the position these plants occupy in the practice of medicine today.

In our country, the cost of imported medicine is becoming prohibitive. This shows us clearly the urgent need for extensive research on our medicinal plants. Never before had we been so forced to rely upon our own resources as we are then when the very life of our nation (for people are the nation) depended upon the herbs that God had graciously given us.

LAGUNDI IS A SPARK AND WE HOPE THIS SPARK SHALL START A FLAME.

Appendix A

Grading of Asthma

Grade 1A

Patient only able to carry housework or job with great difficulty. Sleep frequently disturbed.

Grade 1B

Patient only able to carry housework or job with great difficulty. Sleep frequenty disturbed.

Grade 2A

Patient confined to chair or bed but able to get up with moderate difficulty. Sleep is disturbed with little or no relief from inhaler.

Grade 2B

Patient confined to chair or bed and only able to get up with great difficulty. Unable to sleep. Pulse rate over 120 per minute.

Grade 3

Patient totally confined to chair or bed. No sleep. No relief from inhaler. Pulse rate over 120 per minute.

Grade 4

Patient immobilized and completely exhausted.

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NSTA – Project 7711
PCHRD

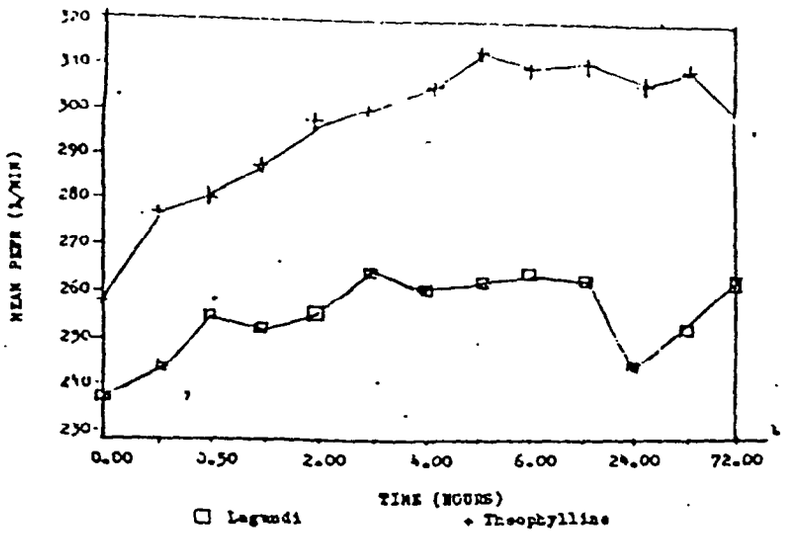

FIG. 1. MEAN PEFR VALUES OF LAGUNDI AND THEOPHYLLINE TREATED GROUPS OVER TIME

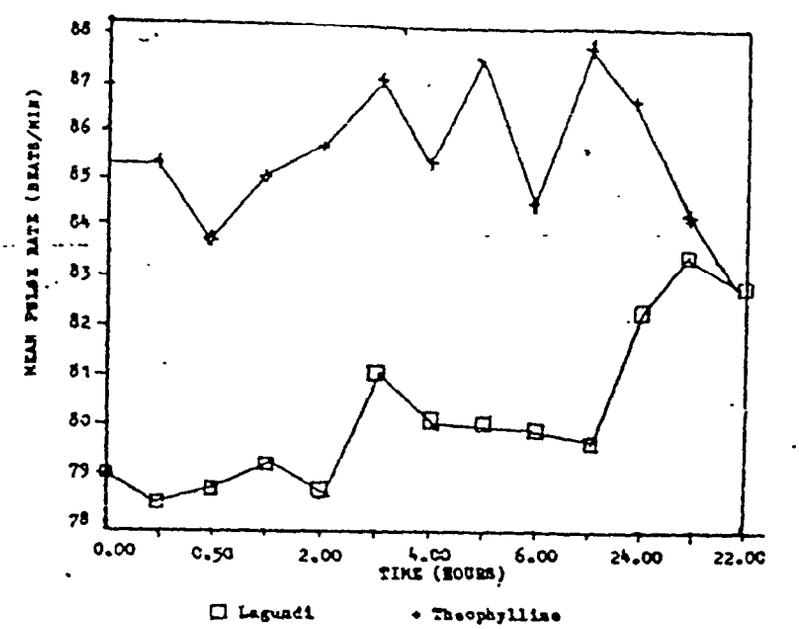

FIG. 2. MEAN PULSE RATE OF LAGUNDI AND THEOPHYLLINE TREATED GROUPS OVER TIME

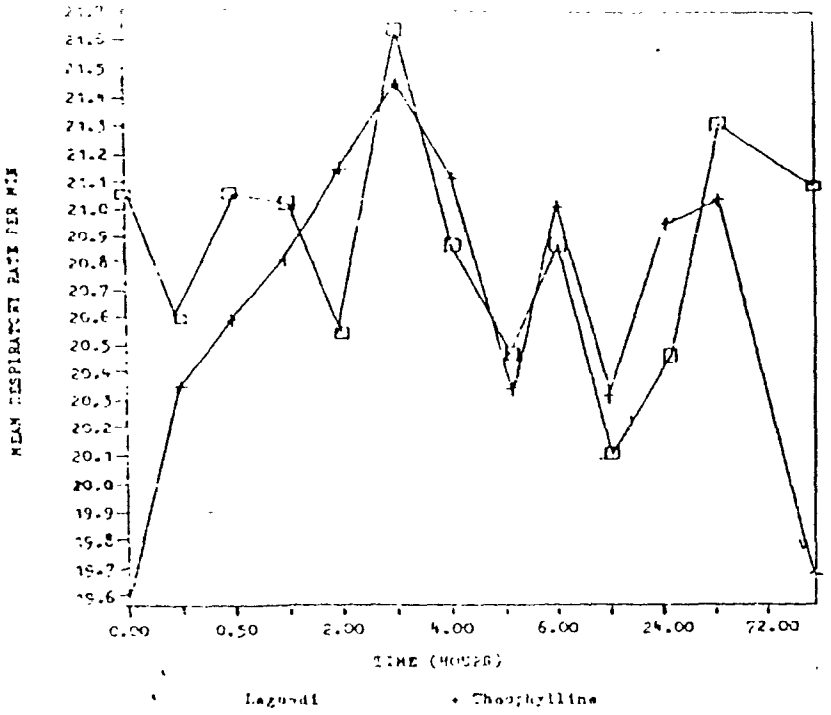

FIG. 3. MEAN RESPIRATORY RATE OF LAGUNDI AND THEOPHYLLINE GROUPS OVER TIME

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SUBMITTED CLINICAL STUDY
REDACTED IN ITS ENTIRETY
CONTAINS
CONFIDENTIAL COMMERICAL INFORMATION

Copy Vitex negundo L. - BioVitaflu/Biovitabronch

From:
Mary Ann Coral-Amasifuen
Kelatron Corporation World Headquarters
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Ogden, Utah 8440 |
Phone (801) 394-4558

Kelatron Corporation Botanical Division
2145 Barefoot Park, SW
Wilson, North Carolina 27893
Phone: (252) 234-7160

To:
Office of Nutritional Products
Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

In accordance with:
TITLE: 21 Food And Drugs
Chapter I – Food and Drug Administration
Dept of Health and Human Services
Part 190 – Dietary Supplements
Subpart B—New Dietary ingredient Notification
Sec. 190.6 Requirement for premarket notification

(1) **Name and address of distributor**: Kelatron Corporation
1675 West 2750 South
Ogden, Utah 84401

(2) **Name of new dietary ingredient:** BioVitaflu / BioVitabronch (*Vitex negundo*, L)

(3) **Description of new ingredient:** BioVitaflu / BioVitabronch is the bulk pure leaf powder of the plant variety *Vitex negundo,* L. harvested for medicinal purposes in the Philippines. There has been clinical research done on the effectiveness of this plant for enhancing air flow in and out of lungs and reducing phlegm caused by congestion in the lungs. It is currently in use in the Asian market under the name Lagundi, which is the local name for the plant in southeast Asia.

(3) (i) **Level of new ingredient**: The product contains only the pure plant leaf powder of *Vitex negundo*, L and no other substance, to be sold in bulk powder form to retail manufacturers.

(3) (ii) **Condition of use**: Clinical trials indicated that BioVitaflu/BioVitabronch may be effective in relaxing smooth muscle tissue and ease night time coughing.

(4) **History of use**: *see attachment 4A*

(5) **Signature** _____ **Date** 12-10-01

RECEIVED 1/3/02

ATTACH 4A

REPUBLIC OF THE PHILIPPINES
DEPARTMENT OF HEALTH
BUREAU OF FOOD AND DRUGS
Alabang, Muntinlupa
Metro Manila

Nº 29690

P.S.D. Form No. 1
Registration Status :
BFAD Registration No. : HDL-36
Classification Otc-initial

CERTIFICATE OF PRODUCT REGISTRATION

Pursuant to the provisions of Republic Act No. 3720 as amended, known as the Foods, Drugs and Devices and Cosmetics Act, and consistent with R.A. 6675, known as the Generic Act of 1988, the product more particularly described hereunder has been found to conform with requirements and standards for registration of pharmaceutical products per A.O. No. 67 s. 1989.

Name of Products : Generic : LAGUNDI 600 mg TABLET
Vitex negundo L. (Fam. Verbenaceae)

Brand (if any) : ASCOF FORTE 600 mg TABLET

Manufacturer / Trader : Pascual Laboratories Inc.
Balagtas, Bulacan

Approved Indication (s) : For the treatment of bronchospasm in acute bronchial asthma, chronic bronchitis and other broncho pulmonary disorders.

Claimed Stability : 24 months

This registration shall be valid for five year(s) and shall expire on Sept. 09, 2003 subject to the following conditions:

CERTIFIED TRUE COPY:
JONATHAN P. ROMAGOS
Special Authenticating Officer
BUREAU OF FOOD AND DRUGS
Date: 9-22-98
VALID WITHOUT OFFICIAL SEAL

No change in the formulation, labelling and commercial presentation of this product shall be made during the effectivity of this registration without the approval of this Office.

This registration is subject to suspension, cancellatoin or recall should violation of any provision of R.A. 3720, as amended, and/or regulations issued thereunder involving the product be committed.

Witness My Hand and Seal of this Office, this 09th day of September, 1998

SL (Cellofoil)
P6,420
9975454
97A-305/GIM/cora

QUINTIN L. KINTANAR, M.D., Ph. D.
Director - CESO I

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